Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Cystic fibrosis: diagnosis and management.

Bibliographic Source(s)

National Guideline Alliance. Cystic fibrosis: diagnosis and management. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct 25. 42 p. (NICE guideline; no. 78).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
	Patient and Public Perspectives

	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▯▯	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▮▮▮	External Review
▮▮▮▮▮	Updating

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Alliance (NGA) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Diagnosis of Cystic Fibrosis

Be aware that cystic fibrosis can be diagnosed based on:

- Positive test results in people with no symptoms, for example infant screening (blood spot immunoreactive trypsin test) followed by sweat and gene tests for confirmation or
- Clinical manifestations, supported by sweat or gene test results for confirmation
- Clinical manifestations alone, in the rare case of people with symptoms who have normal sweat or gene test results.

Assess for cystic fibrosis and, when clinically appropriate, perform a sweat test (for children and young people) or a cystic fibrosis gene test (for adults) in people with any of the following:

- Family history
- Congenital intestinal atresia
- Meconium ileus

- Symptoms and signs that suggest distal intestinal obstruction syndrome
- Faltering growth (in infants and young children)
- Undernutrition
- Recurrent and chronic pulmonary disease, such as:
  - Recurrent lower respiratory tract infections
  - Clinical or radiological evidence of lung disease (in particular bronchiectasis)
  - Persistent chest X-ray changes
  - Chronic wet or productive cough
- Chronic sinus disease
- Obstructive azoospermia (in young people and adults)
- Acute or chronic pancreatitis
- Malabsorption
- Rectal prolapse (in children)
- Pseudo-Bartter syndrome.

Refer people with suspected cystic fibrosis to a specialist cystic fibrosis centre if:

- They have a positive or equivocal sweat test result
- Their assessment suggests they have cystic fibrosis but their test results are normal
- Gene testing reveals 1 or more cystic fibrosis mutations.

Information and Support

Provide people who are newly diagnosed with cystic fibrosis and their family members or carers (as appropriate) with opportunities to discuss their concerns.

Information and support should be provided by healthcare professionals with expertise in cystic fibrosis.

Provide people with suspected or diagnosed cystic fibrosis and their family members or carers (as appropriate) with relevant information that they can understand, and opportunities for discussion on topics such as:

- Their diagnosis
- Monitoring of their condition
- Management choices for their condition
- Possible or existing complications or comorbidities
- Implications for living independently.

Provide people with cystic fibrosis and their family members or carers (as appropriate) with information about their care pathway.

Give information to people with cystic fibrosis and to family members or carers in ways that are individually appropriate. Avoid jargon and use formats that they prefer, for example:

- Face-to-face discussions
- Copies of correspondence
- Written information (such as leaflets)
- Any digital media and reliable internet sources that are available.

When appropriate, provide people with cystic fibrosis and their family members or carers with opportunities for discussion with relevant expert professionals on:

- Available resources and support, such as local support and advocacy services
- Managing the risks of cross-infection
- Implications of the condition for school and education
- Career planning
- Transition to adult care
- Foreign travel

- Fertility and contraception
- Pregnancy and parenting
- Organ transplantation
- End of life care.

Provide people with cystic fibrosis with information about how to contact other people with cystic fibrosis without risking cross-infection (see "Preventing Cross-infection," below), for example by directing them to online support groups.

For more information on communication, providing information and shared decision-making in adult NHS services, see the NICE guideline Patient experience in adult NHS services: improving the experience of care for people using adult NHS services .

Be aware that people with cystic fibrosis and their family members or carers will need emotional support and some may need specialist psychological support (see "Psychological Assessment," below), in particular:

- At diagnosis
- At times of transition (for example, when starting or changing school, moving from education to work, or changing to living independently for the first time)
- In relation to fertility, including family planning, pregnancy and infertility
- To cope with complications of cystic fibrosis
- When waiting for or having organ transplantation
- When approaching the end of life.

Service Delivery

Service Configuration

Care for people with cystic fibrosis should be provided by a specialist cystic fibrosis multidisciplinary team based at a specialist cystic fibrosis centre (see "Multidisciplinary Team," below).

Specialist cystic fibrosis centres should:

- Plan patient care (including outpatient and inpatient care), taking into account the risk of cross-infection (see "Preventing Cross-infection," below)
- Maintain local and national registers of patients that include information about their clinical condition, treatment and outcomes
- Audit practice and outcomes.

When a shared-care model is used for children and young people, it should include:

- Formal arrangements between the local paediatric team at the shared-care centre and the multidisciplinary team at the specialist cystic fibrosis centre
- Direct involvement of specialist cystic fibrosis multidisciplinary team members
- An annual assessment and at least one other review per year by the specialist cystic fibrosis multidisciplinary team, in addition to reviews by the local paediatric team (see "Annual and Routine Reviews," below).

If available and when clinically appropriate, outreach care for adults with cystic fibrosis may be provided by the specialist cystic fibrosis multidisciplinary team at a local hospital.

The specialist cystic fibrosis centre should have a point of contact available at all times (day or night) for urgent enquiries from people with cystic fibrosis and their family members or carers (as appropriate).

Consider telemedicine or home visits for routine monitoring when they are more appropriate than outpatient visits and if the person with cystic fibrosis prefers it.

Make arrangements (including providing equipment and expert support) for people to have intravenous

antibiotic therapy at home, when this is appropriate.

Multidisciplinary Team

The specialist cystic fibrosis multidisciplinary team should include at least one of each (depending on the size of the clinic) of the following professionals, who should have specialist expertise in the condition:

- Specialist paediatricians or adult physicians
- Specialist nurses
- Specialist physiotherapists
- Specialist dietitians
- Specialist pharmacists
- Specialist clinical psychologists.

The specialist cystic fibrosis multidisciplinary team should be led by a specialist paediatrician or adult physician.

The specialist cystic fibrosis multidisciplinary team should either include or have access to social workers.

Social workers should provide advice and support to people with cystic fibrosis and their family members or carers (as appropriate), for example on:

- Help with adjusting to long-term treatment (such as taking regular medicines)
- Education
- Employment
- Government benefits
- Respite care.

Specialist nurses (working with specialist paediatricians or physicians) should coordinate care and facilitate communication between other members of the cystic fibrosis team, and act as advocates for people with cystic fibrosis and their family members or carers (as appropriate). Key clinical roles could include:

- Support during and after diagnosis and when starting treatment
- Triage
- Advanced clinical assessment
- Coordinating home intravenous antibiotic services, including intravenous access.

Specialist physiotherapists should assess and advise people with cystic fibrosis at clinic, at inpatient admissions, during pulmonary exacerbations and at their annual review. Assessment and advice could cover airway clearance, nebuliser use, musculoskeletal disorders, exercise, physical activity and urinary incontinence.

Specialist dietitians should assess and advise people with cystic fibrosis about all aspects of nutrition at outpatient clinic visits, during inpatient admissions and at their annual review (see "Nutritional Interventions," below).

Specialist pharmacists should advise people with cystic fibrosis on medicines optimisation at outpatient clinic visits, during inpatient admissions, on discharge from hospital and at annual review. They should advise healthcare professionals on all aspects of medicines use and prescribing, and support general practitioners (GPs), community pharmacists and homecare providers to ensure that people with cystic fibrosis get the medicines they need without interruption.

Specialist clinical psychologists should assess and advise people with cystic fibrosis and their family members or carers (as appropriate) at outpatient clinic visits and (if needed) at other outpatient appointments, during inpatient admissions, and at their annual review (see "Psychological Assessment," below).

The specialist cystic fibrosis multidisciplinary team should either include or have access to specialist

expertise relevant to cystic fibrosis in the following areas:

- Microbiology
- Pulmonary physiology
- Diabetes
- Gastroenterology
- Hepatology
- Rheumatology
- Psychiatry
- Interventional radiology
- Surgery (gastrointestinal, thoracic, and ear, nose and throat)
- Obstetrics
- Palliative care.

The specialist cystic fibrosis multidisciplinary team should work with GPs, and provide timely information so that GPs can support people with cystic fibrosis by:

- Prescribing cystic fibrosis medicines:
  - In batches of at least 1 month at a time for routine medicines
  - Or longer periods if advised by the specialist team
  - Following guidance on arrangements for prescriptions of unlicensed medicines
- Providing routine annual immunisation, including any alterations for people with cystic fibrosis and flu vaccinations for family members and carers
- Managing health problems not related to cystic fibrosis
- Certification of illnesses
- Working in partnership with cystic fibrosis homecare teams, particularly for end of life care
- Providing care for the person's family members or carers.

Transition to Adult Services

Begin discussing the transition process to adult services with young people with cystic fibrosis when they are 12 years old, and with their family members or carers (as appropriate).

All cystic fibrosis services should have a coordinated and documented pathway for transition from children's to adults' services that includes plans for managing all cystic-fibrosis-related aspects of care.

Ask people with cystic fibrosis and their family members or carers (as appropriate) for feedback on the quality of the transition service, taking account of the section on planning and developing transition services in the NICE guideline Transition from children's to adults' services for young people using health or social care services .

For more guidance on managing transition from children's to adults' services, see the NICE guideline Transition from children's to adults' services for young people using health or social care services . In particular, see the sections on:

- Transition planning, for guidance on when transition should happen
- Named workers
- Overarching principles, for guidance on joint responsibility and working together with other organisations.

Complications of Cystic Fibrosis

Be aware that people with cystic fibrosis are at risk of the following common complications:

- Being underweight
- Meconium ileus (affects 1 in 7 newborn babies)
- Fat-soluble vitamin deficiencies (including vitamins A, D, E and K)
- Distal intestinal obstruction syndrome

Muscle pains and arthralgia
Male infertility caused by obstructive azoospermia (almost all males with cystic fibrosis are infertile)
Reduced female fertility
Upper airway complications, including nasal polyps and sinusitis (prevalence increases with age)
Chronic liver disease (the prevalence increases with age until early adulthood)
Urinary stress incontinence
Cystic-fibrosis-related diabetes (uncommon in children under 10 years, but the prevalence increases with age and it affects up to 1 in 2 adults)
Reduced bone mineral density (including osteoporosis).

Be aware that people with cystic fibrosis are at risk of the following less common complications:

Cystic-fibrosis-related arthritis
Delayed puberty (associated with severe cystic fibrosis)
Renal calculi (incidence increases with age and 1 in 20 adults are affected).

Annual and Routine Reviews

Be aware that:

The aim of cystic fibrosis care is to prevent or limit symptoms and complications of the condition
Routine monitoring and annual assessments are crucial in providing effective care.

Offer people with cystic fibrosis a comprehensive annual review that includes the following:

A pulmonary assessment (see "Pulmonary Monitoring," below)
An assessment of nutrition and intestinal absorption (see "Nutritional Interventions and Exocrine Pancreatic Insufficiency," below)
An assessment for liver disease (see "Liver Disease," below)
Testing for cystic-fibrosis-related diabetes, from 10 years of age (see "Cystic-fibrosis-related Diabetes," below)
An assessment for other potential or existing cystic fibrosis complications (see "Complications of Cystic Fibrosis," above)
A psychological assessment (see "Psychological Assessment," below)
Assessments by a specialist nurse, physiotherapist, pharmacist and social worker (see "Service Delivery," above)
A review of their exercise programme (see "Exercise," below).

Provide regular routine reviews for people with cystic fibrosis, and do these more frequently immediately after diagnosis and in early life. For example:

Weekly in their first month of life
Every 4 weeks when they are between 1 and 12 months old
Every 6 to 8 weeks when they are between 1 and 5 years old
Every 8 to 12 weeks when they are over 5 years old
Every 3 to 6 months as adults.

Pulmonary Monitoring, Assessment and Management

Pulmonary Monitoring

For people with cystic fibrosis who have clinical evidence of lung disease, base the frequency of routine reviews on their clinical condition but review children and young people at least every 8 weeks and adults at least every 3 months. If appropriate, think about using the review schedules in the previous recommendation.

Include the following at each routine review, in relation to pulmonary assessment, for people with cystic fibrosis:

- A clinical assessment, including a review of clinical history and medicines adherence, and a physical examination with measurement of weight and length or height
- Measurement of oxygen saturation
- Taking respiratory secretion samples for microbiological investigations, using sputum samples if possible, or a cough swab or nasal pharyngeal aspirate (NPA)
- Lung function testing with spirometry (including forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and forced expiratory flow [FEF] 25%–75%) in adults, and in children and young people who can do this.

If spirometry is normal at a routine review, consider measuring lung clearance index.

Include the following at each annual review in relation to pulmonary assessment for people with cystic fibrosis:

- A clinical assessment, including a review of the clinical history and medicines adherence, and a physical examination, with measurement of weight and length or height
- A physiotherapy assessment
- Measurement of oxygen saturation
- A chest X-ray
- Blood tests, including white cell count, aspergillus serology and serum IgE
- Taking respiratory secretion samples for microbiological investigations (including non-tuberculous mycobacteria)
- Lung function testing (for example with spirometry, including FEV_1, FVC, and FEF 25%–75%) in adults, and in children and young people who can do this.

Consider measuring lung clearance index at each annual review if spirometry is normal.

For people with cystic fibrosis with lung disease who have symptoms that are concerning them or their family members or carers (as appropriate), consider which of the following may be useful:

- Review of clinical history
- Physical examination, including measurement of weight and length or height
- Measurement of oxygen saturation
- Taking respiratory secretion samples for microbiological investigations, using sputum samples if possible, or a cough swab or NPA if not
- For adults, blood tests to measure white cell count and inflammatory markers such as Câ€˜reactive protein
- Lung function testing, for example with spirometry (including FEV_1, FVC, and FEF 25%–75%) in adults, and in children and young people who can do this
- Lung clearance index for people with normal spirometry results.

Depending on the assessments that are needed, decide whether to provide a remote telemedicine or face-to-face assessment.

Think about doing a low-dose chest computed tomography (CT) scan for children with cystic fibrosis who have not had a chest CT scan before, to detect features that other tests (such as a plain chest X-ray) would miss (for example early bronchiectasis).

Think about doing a chest X-ray for people with cystic fibrosis during or after treatment for an exacerbation of lung disease (taking account of severity), if:

- The exacerbation does not respond to treatment or
- A chest X-ray before treatment showed new radiological abnormalities.

Monitor the treatment response during and after an exacerbation of lung disease by assessing whether the symptoms and signs have resolved, and as appropriate:

- Take respiratory secretion samples for microbiological investigations, using sputum samples if

possible, or a cough swab or NPA if not
Test lung function, for example with spirometry (including FEV_1, FVC and FEF 25%–75%) in adults, and in children and young people who can do this
Measure oxygen saturation.

Think about using broncho-alveolar lavage to obtain airway samples for microbiological investigation in people with cystic fibrosis if:

They have lung disease that has not responded adequately to treatment and
The cause of the disease cannot be found with non-invasive upper airway respiratory secretion sampling (including sputum induction if appropriate).

Airway Clearance Techniques

Discuss the use of airway clearance techniques with people with cystic fibrosis who do not have clinical evidence of lung disease and their parents or carers (as appropriate). Provide them with training in airway clearance techniques and explain when to use them.

Offer training in airway clearance techniques to people with cystic fibrosis who have clinical evidence of lung disease and their parents or carers (as appropriate).

When choosing an airway clearance technique for people with cystic fibrosis:

Assess their ability to clear mucus from their lungs, and offer an individualised plan to optimise this
Take account of their preferences and (if appropriate) those of their parents and carers
Take account of any factors that may influence adherence.

Regularly assess the effectiveness of airway clearance techniques, and modify the technique or use a different one if needed.

Do not offer high-frequency chest wall oscillation as an airway clearance technique for people with cystic fibrosis except in exceptional clinical circumstances. The specialist cystic fibrosis team will decide whether these circumstances apply, and their decision would then be subject to the NHS England policy on Individual Funding Requests. Be aware that the evidence shows high-frequency chest wall oscillation is not as effective as other airway clearance techniques.

Consider using non-invasive ventilation in people with cystic fibrosis who have moderate or severe lung disease and cannot clear their lungs using standard airway clearance techniques.

Mucoactive Agents

Offer a mucoactive agent to people with cystic fibrosis who have clinical evidence of lung disease.

Offer rhDNase (dornase alfa; recombinant human deoxyribonuclease) as the first choice of mucoactive agent. (At the time of publication [October 2017], rhDNase did not have a UK marketing authorisation for use in children under 5 years of age with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

If clinical evaluation or lung function testing indicates an inadequate response to rhDNase, consider both rhDNase and hypertonic sodium chloride or hypertonic sodium chloride alone. (At the time of publication [October 2017], rhDNase did not have a UK marketing authorisation for use in children under 5 years of age with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Consider mannitol dry powder for inhalation for children and young people who cannot use rhDNase and

hypertonic sodium chloride because of ineligibility, intolerance or inadequate response. (At the time of publication [October 2017], mannitol dry powder for inhalation did not have a UK marketing authorisation for use in children with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:

- Who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and Whose lung function is rapidly declining (FEV_1 decline greater than 2% annually) and
- For whom other osmotic agents are not considered appropriate.

This recommendation is from Mannitol dry powder for inhalation for treating cystic fibrosis (NICE technology appraisal guidance 266).

People currently receiving mannitol whose cystic fibrosis does not meet the criteria in the previous recommendation should be able to continue treatment until they and their clinician consider it appropriate to stop.

This recommendation is from Mannitol dry powder for inhalation for treating cystic fibrosis (NICE technology appraisal guidance 266).

For recommendations on using lumacaftor–ivacaftor, see the NICE technology appraisal guidance on Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.

Pulmonary Infection

Staphylococcus aureus

Offer flucloxacillin as antibiotic prophylaxis against respiratory *Staphylococcus aureus* infection for children with cystic fibrosis from the point of diagnosis up to age 3, and consider continuing up to 6 years of age. Before starting flucloxacillin, discuss the uncertainties and possible adverse effects with their parents or carers (as appropriate). For children who are allergic to penicillins, consider an alternative oral anti-*Staphylococcus aureus* agent. (At the time of publication [October 2017], flucloxacillin did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

For children who are taking antibiotic prophylaxis and have a respiratory sample culture that is positive for *Staphylococcus aureus*:

- Review prophylaxis adherence and help the child's parents or carers (as appropriate) with any difficulties they are having
- Start treatment-dose anti-*Staphylococcus aureus* antibiotics
- Restart prophylaxis after treatment, even if treatment has not been successful.

For people who are not taking prophylaxis and have a new *Staphylococcus aureus* infection (that is, previous respiratory sample cultures did not show *Staphylococcus aureus* infection):

- If they are clinically well, consider an oral anti-*Staphylococcus aureus* agent
- If they are clinically unwell and have pulmonary disease, consider oral or intravenous (depending on infection severity) broad-spectrum antibiotics that include an anti-*Staphylococcus aureus* agent.

Consider a long-term antibiotic to suppress chronic methicillin-sensitive *Staphylococcus aureus* (MSSA) respiratory infection in people whose pulmonary disease is stable.

For people with chronic MSSA respiratory infection who become clinically unwell with pulmonary disease, consider oral or intravenous broad-spectrum antibiotics (depending on infection severity) that include an anti-*Staphylococcus aureus* agent.

For people with new evidence of methicillin-resistant *Staphylococcus aureus* (MRSA) respiratory infection (with or without pulmonary exacerbation), seek specialist microbiological advice on treatment.

Do not routinely use antibiotics to suppress chronic MRSA in people with stable pulmonary disease.

If a person with cystic fibrosis and chronic MRSA respiratory infection becomes unwell with a pulmonary exacerbation or shows a decline in pulmonary function, seek specialist microbiological advice.

For guidance on preventing the spread of infection, refer to the NICE guideline Healthcare-associated infections: prevention and control in primary and community care .

Pseudomonas aeruginosa

If a person with cystic fibrosis develops a new *Pseudomonas aeruginosa* infection (that is, recent respiratory secretion sample cultures showed no infection):

- If they are clinically well:
  - Commence eradication therapy with a course of oral or intravenous antibiotics, together with an inhaled antibiotic
  - Follow this with an extended course of oral and inhaled antibiotics
- If they are clinically unwell:
  - Commence eradication therapy with a course of intravenous antibiotics together with an inhaled antibiotic
  - Follow this with an extended course of oral and inhaled antibiotics.

If eradication treatment is not successful despite treatment as recommended in the previous recommendation, offer sustained treatment with an inhaled antibiotic. Consider nebulised colistimethate sodium as first-line treatment. (See recommendation below on using colistimethate dry powder for inhalation.)

Depending on infection severity, use either an oral antibiotic or a combination of 2 intravenous antibiotics of different classes for people:

- Who have chronic *Pseudomonas aeruginosa* infection (when treatment has not eradicated the infection) and
- Who become clinically unwell with a pulmonary disease exacerbation.

If a person with chronic *Pseudomonas aeruginosa* infection repeatedly becomes clinically unwell with pulmonary disease exacerbations, consider changing the antibiotic regimens used to treat exacerbations.

Colistimethate sodium dry powder for inhalation (DPI) is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with cystic fibrosis only if:

- They would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered and
- The manufacturer provides colistimethate sodium DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

This recommendation is from Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal guidance 276).

For people with chronic *Pseudomonas aeruginosa* infection who are clinically deteriorating despite regular inhaled colistimethate sodium, consider nebulised aztreonam, nebulised tobramycin, or tobramycin DPI (see next recommendation on using tobramycin DPI). (At the time of publication [October 2017], Colistimethate sodium DPI, nebulised tobramycin, tobramycin DPI and nebulised aztreonam and nebulised

tobramycin did not have a UK marketing authorisation for use in children under 6 with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Tobramycin DPI is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with cystic fibrosis only if:

- Nebulised tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated, is not tolerated or has not produced an adequate clinical response and
- The manufacturer provides tobramycin DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

This recommendation is from Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal guidance 276).

People currently using tobramycin DPI or colistimethate sodium DPI that is not recommended according to the preceding recommendations should be able to continue treatment until they and their clinician consider it appropriate to stop. For children and young people this decision should be made jointly by the clinician, the child or young person and their parents or carers.

This recommendation is from Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal guidance 276).

Burkholderia cepacia Complex

For people with cystic fibrosis who develop a new *Burkholderia cepacia* complex infection (that is, recent respiratory sample cultures showed no *Burkholderia cepacia* infection):

- Whether they are clinically well or not, give antibiotic eradication therapy using a combination of intravenous antibiotics
- Seek specialist microbiological advice on the choice of antibiotics to use.

Be aware that there is no evidence to support using antibiotics to suppress chronic *Burkholderia cepacia* complex infection in people with cystic fibrosis who have stable pulmonary status. Discuss the possible risks (for example drug toxicity) of treating the infection with the person and their family members or carers (as appropriate).

For people with cystic fibrosis who have chronic *Burkholderia cepacia* complex infection (when treatment has not eradicated the infection) and who become clinically unwell with a pulmonary disease exacerbation:

- Give a combination of oral or intravenous antibiotics
- Seek specialist microbiological advice on which antibiotics to use.

For people with cystic fibrosis who have chronic *Burkholderia cepacia* complex infection and declining pulmonary status:

- Consider sustained treatment with an inhaled antibiotic to suppress the infection
- Seek specialist microbiological advice on which antibiotic to use
- Stop this treatment if there is no observed benefit.

Haemophilus influenzae

For people with cystic fibrosis who develop a *Haemophilus influenzae* infection (diagnosed by a positive respiratory sample culture) but do not have clinical evidence of pulmonary infection, treat with an appropriate oral antibiotic.

For people with cystic fibrosis who develop a *Haemophilus influenzae* infection (diagnosed by a positive respiratory sample culture) and are unwell with clinical evidence of pulmonary infection, treat with an appropriate antibiotic, given orally or intravenously depending on the severity of the illness.

Non-tuberculous mycobacteria

For people with cystic fibrosis who are clinically well but whose airway secretions are persistently positive for non-tuberculous mycobacteria, discuss with them and their family members or carers (as appropriate):

- The clinical uncertainties about non-tuberculous mycobacterial infection and
- The possible benefits and risks (for example, drug toxicity) of treating it.

If a person with cystic fibrosis has a respiratory sample test positive for new non-tuberculous mycobacteria infection, repeat the test for confirmation.

If repeat testing confirms persistent non-tuberculous mycobacteria, do a chest CT scan to look for changes consistent with non-tuberculous mycobacteria disease.

Consider non-tuberculous mycobacterial therapy aimed at eradication for people with cystic fibrosis:

- Whose airway secretions persistently test positive for non-tuberculous mycobacteria and
- Who are clinically unwell with pulmonary disease, or who have a chest CT scan showing changes consistent with non-tuberculous mycobacteria disease and
- Whose pulmonary disease has not responded to other recommended treatments.

Seek specialist microbiological advice on which antibiotics to use and on the duration of treatment.

Aspergillus fumigatus Complex

Do not routinely use antifungal agents to suppress chronic *Aspergillus fumigatus* complex respiratory infection (diagnosed by persistently positive respiratory secretion sample cultures) in people with cystic fibrosis and stable pulmonary status.

For people with cystic fibrosis with chronic *Aspergillus fumigatus* complex respiratory infection and declining pulmonary status:

- Consider sustained treatment with an antifungal agent to suppress the infection
- Seek specialist microbiological advice on which antifungal agent to use
- Stop treatment or change to a different agent if there is no benefit.

For people with cystic fibrosis with elevated aspergillus serology (aspergillus-specific immunoglobulin G [IgG] and/or immunoglobulin E [IgE]) and declining pulmonary function despite optimised pulmonary treatment, think about treating for allergic bronchopulmonary aspergillosis or other aspergillus airway disease, especially if there are consistent chest X-ray or CT scan changes.

Unidentified Infections

For people with cystic fibrosis who have a pulmonary disease exacerbation and no clear cause (based on recent respiratory secretion sample cultures):

- Use an oral or intravenous (depending on the exacerbation severity) broad-spectrum antibiotic
- Continue collecting respiratory secretion samples, and change treatments if a pathogen is identified and a more appropriate treatment is available.

Immunomodulatory Agents

For people with cystic fibrosis and deteriorating lung function or repeated pulmonary exacerbations, offer long-term treatment with azithromycin at an immunomodulatory dose. (At the time of publication [October 2017], azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing

unlicensed medicines for further information.)

For people who have continued deterioration in lung function, or continuing pulmonary exacerbations while receiving long-term treatment with azithromycin, stop azithromycin and consider oral corticosteroids.

Do not offer inhaled corticosteroids as an immunomodulatory treatment for cystic fibrosis.

Other Monitoring, Assessment and Management

Nutritional Interventions and Exocrine Pancreatic Insufficiency

The cystic fibrosis specialist dietitian should offer advice on the benefits of optimal nutrition, and at the annual assessment review the person's:

- Total nutritional intake, including energy intake (calories)
- Estimated nutritional needs
- Pancreatic enzyme replacement therapy, if appropriate.

Encourage people to increase calorie intake by increasing portion size and eating high-energy foods if there is concern about their nutrition (including weight loss and inadequate weight gain).

If increased portion size and high-energy foods are not effective, consider a trial of oral nutritional supplements.

If attempts to increase calorie intake are not effective, consider:

- Supplementation with enteral tube feeding or
- For adults, a short-term trial of an appetite stimulant (for example up to 3 months). (At the time of publication [October 2017], appetite stimulants did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Test for exocrine pancreatic insufficiency in people with cystic fibrosis, using a non-invasive technique such as stool elastase estimation. If the test result is normal, repeat it if symptoms or signs suggesting malabsorption occur.

Offer oral pancreatic enzyme replacement therapy to people with exocrine pancreatic insufficiency. Adjust the dose as needed to minimise any symptoms or signs of malabsorption.

Consider an acid suppression agent (for example an H_2 receptor antagonist or a proton pump inhibitor) for people who have persistent symptoms or signs of malabsorption despite optimal pancreatic enzyme replacement therapy. (At the time of publication [October 2017], acid suppression agents did not have a UK marketing authorisation for use in people with cystic fibrosis for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Distal Intestinal Obstruction Syndrome

Be aware that a variety of conditions can cause acute abdominal pain and resemble distal intestinal obstruction syndrome in people with cystic fibrosis, for example:

- Constipation
- Appendicitis
- Intussusception
- Cholecystitis.

Suspect distal intestinal obstruction syndrome in people with cystic fibrosis who have an acute onset of peri-umbilical or right lower quadrant abdominal pain and any of the following:

- A palpable mass in the right lower quadrant
- Faecal loading in the right lower quadrant on a plain abdominal X-ray, especially if associated with small intestine air-fluid levels
- Clinical features of partial or complete intestinal obstruction, such as vomiting (especially bilious) and abdominal distension.

For people who have an acute onset of peri-umbilical abdominal pain but no other clinical or radiological features of distal intestinal obstruction syndrome, consider further imaging, for example with an:

- Abdominal ultrasound scan or
- Abdominal CT scan.

Manage suspected distal intestinal obstruction syndrome in a specialist cystic fibrosis centre, with supervision from specialists who have expertise in recognising and treating the condition and its complications.

Offer oral or intravenous fluids to ensure adequate hydration (and rehydration if needed) for people with distal intestinal obstruction syndrome.

Consider diatrizoate meglumine and diatrizoate sodium solution (Gastrografin) (orally or via an enteral tube) as first-line treatment for distal intestinal obstruction syndrome.

If diatrizoate meglumine and diatrizoate sodium solution (Gastrografin) is not effective, consider an iso-osmotic polyethylene glycol and electrolyte (PEG) solution (macrogols) (orally or via an enteral tube) as a second-line treatment.

Consider surgery as a last resort, if prolonged treatment with a PEG solution is not effective.

To reduce the risk of distal intestinal obstruction syndrome recurring:

- Encourage people to drink plenty of fluids
- Optimise pancreatic enzyme replacement therapy (see "Nutritional Interventions and Exocrine Pancreatic Insufficiency," below)
- Consider advising regular treatment with a stool-softening agent such as lactulose or a PEG solution.

Liver Disease

Perform a clinical assessment and liver function blood tests at the annual review for people with cystic fibrosis.

If liver function blood tests are abnormal, perform a liver ultrasound scan and consider ursodeoxycholic acid treatment. (At the time of publication [October 2017], ursodeoxycholic acid did not have a UK marketing authorisation for adults with cystic fibrosis for this indication. The prescriber should check individual brands for licensing in children and young people and follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.)

Think about stopping ursodeoxycholic acid if liver function blood tests return to normal and clinical assessment and liver ultrasound scan show no liver disease.

If ursodeoxycholic acid is stopped, monitor for re-emergence of liver disease using clinical assessment and liver function blood tests.

Think about referring people with cystic fibrosis to a liver specialist if the liver function blood test results are persistently abnormal despite treatment with ursodeoxycholic acid.

Refer people with cystic fibrosis to a liver specialist if they have any of the following:

- Chronic progressive liver disease, based on clinical assessment, liver function blood tests or the findings on a liver ultrasound scan
- Liver failure, based on clinical assessment and liver function tests
- Portal hypertension, haematemesis, splenomegaly or findings on a liver ultrasound scan.

Cystic-fibrosis-related Diabetes

Diagnose cystic-fibrosis-related diabetes using one of the following:

- Continuous glucose monitoring (CGM)
- Serial glucose testing over several days
- Oral glucose tolerance testing (OGTT) – if OGTT is abnormal perform CGM or serial glucose testing over several days to confirm the diagnosis.

Test for cystic-fibrosis-related diabetes (as detailed in the previous recommendation) in people with cystic fibrosis annually from 10 years of age.

Test for cystic-fibrosis-related diabetes at the end of the first and second trimesters of pregnancy, using CGM or OGTT.

Test for cystic-fibrosis-related diabetes in people with cystic fibrosis who are taking long-term systemic corticosteroids or receiving enteral tube feeding, using CGM or serial glucose monitoring.

Think about testing for cystic-fibrosis-related diabetes in people who still have any of the following despite optimised cystic fibrosis treatment:

- Unexplained weight loss
- A deterioration in lung function as measured by spirometry
- Increased frequency of pulmonary exacerbations
- Excessive tiredness.

Bone Mineral Density

Consider dual energy X-ray absorptiometry (DXA) bone density scans for people with cystic fibrosis who have factors that put them at high risk of low bone mineral density, such as:

- Frequent or long-term oral corticosteroid use
- Frequent intravenous antibiotic use
- Severe lung disease
- Undernutrition
- Previous low-impact fractures
- Previous transplants
- Post menopause.

Seek specialist advice for people with a bone mineral density standard deviation below -2.0 (Z score) or -2.5 (T score).

Exercise

Advise people with cystic fibrosis and their family members or carers (as appropriate) that regular exercise improves both lung function and overall fitness.

Offer people with cystic fibrosis an individualised exercise programme, taking into account their capability and preferences.

Regularly review exercise programmes to monitor the person's progress and ensure that the programme continues to be appropriate for their needs.

Provide people with cystic fibrosis who are having inpatient care with:

An assessment of their exercise capacity
The facilities and support to continue their exercise programme (as appropriate), taking into account the need to prevent cross-infection (see "Preventing Cross-infection," above) and local infection control guidelines.

Psychological Assessment

At the annual review, the specialist clinical psychologist should include assessments of:

General mental health and wellbeing
Quality of life
Any factors that are making treatment adherence difficult
Indicators of emerging psychosocial problems
Behaviours that affect health outcomes.

If a severe mental health condition is identified at any assessment performed by the cystic fibrosis clinical psychologist, refer the person with cystic fibrosis to a mental health practitioner. For guidance on treating mental health conditions, refer to the relevant NICE guideline.

For family members or carers of people with cystic fibrosis, the specialist clinical psychologist should:

Assess any cystic-fibrosis-related needs they have
Support their psychological wellbeing
Refer them to mental health practitioners as needed

Preventing Cross-infection

For recommendations on preventing and controlling infection, see the NICE guidelines Healthcare-associated infections: prevention and control in primary and community care and Healthcare-associated infections: prevention and control, and the NICE quality standard Infection prevention and control.

To prevent cross-infection among people with cystic fibrosis in outpatient and inpatient care, use microbiological surveillance and a local infection control strategy that includes cohorting.

Inform people with cystic fibrosis, their family members or carers (as appropriate) and staff involved in their care about the risk of cross-infection and how to avoid it.

Each specialist cystic fibrosis clinic should be organised to prevent cross-infection. Separate people individually during the clinic, including by organising:

The use of communal areas
Attendance at diagnostic, treatment and pharmacy facilities.

Keep people with transmissible or chronic *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex infection separate from people who do not have these infections, for example by using separate outpatient clinics.

Consider keeping people with cystic fibrosis who have intermittent isolation of *Pseudomonas aeruginosa* separate from people who do not have this infection, for example by using separate outpatient clinics. Help people with cystic fibrosis plan their inpatient attendance to avoid contact with each other, for example when they use:

Hospital restaurants, schools and recreation areas
Diagnostic, treatment and pharmacy facilities (see "Information and Support," above).

During inpatient care, give people with cystic fibrosis individual rooms with en-suite facilities.

Definitions

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally they use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when they are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. They use similar forms of words (for example, 'Do not offer…') when they are confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when they are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

A National Institute for Health and Care Excellence (NICE) pathway titled "Cystic fibrosis overview" is provided on the NICE Web site .

Scope

Disease/Condition(s)

Cystic fibrosis

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Internal Medicine

Pediatrics

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Dietitians

Health Care Providers

Hospitals

Nurses

Patients

Physical Therapists

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Respiratory Care Practitioners

Social Workers

Guideline Objective(s)

To develop a National Institute for Health and Care Excellence (NICE) guideline on the diagnosis and management of cystic fibrosis

Target Population

Infants, children, young people and adults with cystic fibrosis, including those who have non-classic cystic fibrosis and those who have had an organ transplant

Interventions and Practices Considered

1. Diagnosis of cystic fibrosis
    - Clinical manifestations
    - Sweat test
    - Cystic fibrosis gene test
2. Providing information and support
3. Service delivery
    - Service configuration
    - Multidisciplinary team
    - Transition to adult services

4. Awareness of complications of cystic fibrosis
5. Annual and routine reviews
6. Pulmonary monitoring, assessment and management
    - Pulmonary monitoring
    - Airway clearance techniques
    - Use of mucoactive agents
    - Management of pulmonary infection based on infection type
    - Use of immunomodulatory agents
7. Other monitoring, assessment and management
    - Nutritional interventions for exocrine pancreatic insufficiency
    - Management of distal intestinal obstruction syndrome
    - Management of liver disease
    - Management of cystic-fibrosis-related diabetes
    - Monitoring of bone mineral density
    - Exercise
    - Psychological assessment
8. Preventing cross-infection

Major Outcomes Considered

- Health-related quality of life
- Height, weight and body mass index (BMI)
- Survival rates
- Lung function (for example, forced expiratory volume in 1 second [FEV_1])
- Rate of acute pulmonary infections, including those needing hospitalisation
- Prevalence of infection with specific bacterial pathogens
- Patient satisfaction

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Alliance (NGA) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Developing the Review Questions and Outcomes

The review questions were drafted by the NGA, and refined and validated by the guideline committee. The questions were based on the key areas identified in the guideline scope (see Appendix A).

A total of 29 questions were identified (see Table 3 in the full version of the guideline).

The review questions were based on the following frameworks:

Intervention reviews – using population, intervention, comparator and outcome (PICO framework)
Reviews of diagnostic test accuracy – using population, diagnostic test (index tests), reference standard and target condition
Prognostic reviews – using population, presence or absence of a risk factor, and outcome
Prevalence reviews – using population and outcome (prevalence of target condition)
Qualitative reviews – using population, area of interest and themes of interest

These frameworks guided the literature searching process, critical appraisal and synthesis of evidence and facilitated the development of recommendations by the guideline committee.

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Searching for Evidence

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions from January 2015 to September 2016.

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to retrieve only articles published in English. All searches were conducted in MEDLINE, EMBASE and The Cochrane Library. The following searches were updated in January 2017.

Monitoring for liver disease
Airway clearance
Monitoring pulmonary disease
Mucoactive agents
Immunomodulatory agents
Antimicrobials: prophylaxis
Antimicrobials: acute
Antimicrobials: chronic
Nutrition interventions
Exercise
Service configuration: cross-infection
Service configuration: multidisciplinary team (MDT)
Service configuration: models of care

The guideline committee prioritised the list below for re-runs based on the following criteria:

Topics where network meta-analyses (NMAs) and health economic (HE) modelling work have been conducted
Topics with significant evidence movement where it is likely that new evidence will have been published
Topics that are part of the service delivery component of the guideline
Topics with empty reviews (i.e., MDT)
Topics that have been covered earlier in guideline development which may now be at greater risk of being out of date.

Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the group members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix E.

The titles and abstracts of records retrieved by the searches were inspected for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on websites of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. Searches for electronic, ahead-of-print publications were not routinely undertaken unless indicated by the guideline committee. All references suggested by stakeholders at the scoping consultation were initially considered.

Health Economic Literature Search

A global search of economic evidence relating to all treatments for cystic fibrosis was undertaken in April 2015 and re-ran in January 2017. The following databases were searched:

MEDLINE (Ovid);
EMBASE (Ovid);
Cochrane Central Register of Controlled Trials (CCTR);
HTA database (HTA);
NHS Economic Evaluations Database (NHS EED).

Further to the database searches, the committee were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge; reference lists of key identified studies were also reviewed for any potentially relevant studies. Finally, the NICE Web site was searched for any recently published guidance relating to cystic fibrosis that had not been already identified via the database searches.

The search strategy for existing economic evaluations combined terms capturing the target condition (cystic fibrosis) and, for searches undertaken in MEDLINE, EMBASE and CCTR, terms to capture economic evaluations. No restrictions on language or setting were applied to any of the searches, but a standard exclusions filter was applied (letters, animals, etc.). Conference abstracts were considered for inclusion from 1st January 2014, as high-quality studies reported in abstract form before 2014 were expected to have been published in a peer-reviewed journal. Full details of the search strategies are presented in Appendix E.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using pre-defined eligibility criteria defined in Table 4 in the full version of the guideline.

Once the screening of titles and abstracts was complete, full versions of the selected papers were acquired for assessment. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for this search on economic evaluations is presented in Appendix F.

Reviewing Research Evidence

Systematic Review Process

The evidence was reviewed following these steps (see Figure 1 in the full version of the guideline):

Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
Full papers were reviewed against pre-specified inclusion and exclusion criteria in the review protocols (in Appendix D).

Inclusion/Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix D. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix H. In addition, the committee were consulted about any uncertainty regarding inclusion or exclusion.

Type of Studies

Systematic reviews (SRs) with meta-analyses were considered the highest quality evidence to be selected for inclusion.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were prioritised because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Crossover RCTs were appropriate for some of the interventional questions. If there was limited evidence from RCTs, observational studies were included.

For diagnostic reviews, cross-sectional, retrospective or prospective observational studies were considered for inclusion. Where evidence was limited, case-control studies were also considered for inclusion.

For clinical prediction and prognostic reviews, prospective and retrospective cohort studies were included.

For prevalence reviews, the committee prioritised the UK cystic fibrosis (CF) registry. Where no evidence was available or the committee agreed the UK CF registry data provided limited for a particular complication, cross-sectional studies and prospective cohort studies (national registries were preferred) were also included.

For qualitative reviews, studies using focus groups, or structured or semi-structured interviews were considered for inclusion. Survey data or other types of questionnaires were only included if they provided analysis from open-ended questions, but not if they reported descriptive quantitative data only.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Conference abstracts were only considered for inclusion in the absence of full published studies.

Number of Source Documents

See Appendix F: Summary of identified studies (see the "Availability of Companion Documents" field) for information on results of literature searches and the number of included and excluded studies for each review question, including economic article selection.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC) and the National Institute for Health and Care Excellence (NICE): This guideline was developed by the National Institute for Health and Care Excellence (NICE) for the Department of Health. See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Reviewing and Synthesising Research Evidence

Systematic Review Process

The evidence was reviewed following these steps (see Figure 1 in the full version of the guideline):

- Key information was extracted on the study's methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G)
- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual (NICE, 2014) (see the "Availability of Companion Documents" field)
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in committee meetings (details of how the evidence was appraised is described in below and in Section 4.3.5 in the full version of the guideline):
    - Randomised studies: meta-analysis was carried out where appropriate and results were reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for intervention reviews).
    - Observational studies: data were presented individually by study in GRADE profiles.
    - Prognostic studies: data were presented individually by study, usually in terms of the relative effect as reported by the authors.
    - Diagnostic studies: data were presented individually by study as measures of diagnostic test accuracy (sensitivity and specificity, positive and negative likelihood ratios) and were presented in modified GRADE profiles.
    - Prevalence studies: data were presented as measures of prevalence during a period of time (proportions with their 95% confidence intervals); the decision if meta-analysis could be conducted was based on the consideration of the heterogeneity of the studies.
    - Qualitative studies: each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes. These were then presented in GRADE-CERQual (Lewin, 2015) profiles, where CERQual stands for Confidence in the Evidence from Reviews of Qualitative research.

For quality assurance of study identification, either whole study selections or a sample of the study selection results were double checked by a second reviewer. Searches related to the network meta-analysis (NMA) were also double sifted.

A sample of all evidence tables, including a sample of evidence tables related to the NMA were. All drafts of reviews were checked by a second reviewer. Any discrepancies were resolved by discussion between the 2 reviewers.

Types of Data and Methods for Synthesis

Refer to Section 4.3.4 in the full version of the guideline for methods used to synthesise the evidence, including pair-wise and network meta-analyses.

Appraising the Quality of the Evidence by Outcomes

GRADE Methodology

For intervention reviews, the evidence for outcomes from the included randomised controlled trials (RCTs) and observational studies were evaluated and presented using GRADE, which was developed by the

international GRADE working group. Modified GRADE assessments were also carried out for accuracy measures in diagnostic reviews. For the appraisal of the quality of the evidence from qualitative reviews an adapted GRADE-CERQual (Lewin, 2015) approach was used, where CERQual stands for Confidence in the Evidence from Reviews of Qualitative research.

The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The clinical/economic evidence profile tables include details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures of effect and measures of dispersion (such as mean and standard deviation or median and interquartile range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile tables if it was apparent.

The selection of outcomes for each review question was decided when each review protocol was discussed with the committee. However, given the nature of most of the review questions included in this guideline (driven by short- or long-term outcomes), the categorisation of outcomes as critical and important did not follow the standard GRADE approach. The outcomes selected for a review question were critical for decision-making in a specific context.

The evidence for each outcome in interventional reviews was examined separately for the quality elements listed and defined in Table 6 in the full version of the guideline.

The GRADE toolbox is designed only for RCTs and observational studies, but the committee adapted the quality assessment elements and outcome presentation for diagnostic accuracy and qualitative studies, subject to data availability.

For example, for diagnostic accuracy studies, the GRADE tables were modified to include the most appropriate measures of diagnostic accuracy (sensitivity and specificity) (see Table 7 in the full version of the guideline). For prognostic factors, an adapted GRADE approach was conducted. This looked at the body of the evidence for each risk factor across studies for 1 outcome (see Table 8 in the full version of the guideline).

For qualitative studies an adapted GRADE-CERQual (Lewin, 2015) approach was used, where CERQual stands for confidence in the evidence from reviews of qualitative research. This looked at the quality of evidence by theme. These themes may have originated from an individual study or may have been identified through a number of individual themes or components of themes across a number of included studies (see Table 9 in the full version of the guideline).

The main criteria considered in the rating of these elements are discussed below (see Section 4.3.5.2 in the full version of the guideline). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (see the "Rating Scheme for the Strength of the Evidence" field).

Grading the Quality of Clinical Evidence

After results were pooled using data synthesis methods, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using the GRADE approach:

> An initial quality rating was assigned, based on the study design. RCTs start as 'High' in intervention reviews and observational studies as 'Low'. In diagnostic, prognostic and qualitative reviews, evidence from non-randomised studies start as 'High'.
> The rating was then downgraded for the specified criteria: risk of bias (study limitations); inconsistency; indirectness; imprecision; and publication bias. These criteria are detailed in the full version of the guideline. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was a large magnitude of effect or a dose-response gradient,

and if all plausible confounding would reduce a demonstrated effect, or suggest a spurious effect when results showed no effect.

Each quality element considered to have 'serious' or 'very serious' issues was rated down by 1 or 2 points respectively. Value based judgements for relevant interpretation of the levels of quality elements were informed by discussion with the committee for each review to balance consistency of approach across the guideline and clinical relevance within each review (see Table 10 in the full version of the guideline). The downgraded/upgraded ratings were then summed and the overall quality rating was revised, taking into account the relative contributions from the individual studies within a meta-analyses, where performed. For example, RCTs start as high and the overall quality becomes moderate, low or very low if 1, 2 or 3 points are deducted respectively. The reasons or criteria used for downgrading were specified in the footnotes.

For qualitative reviews, each quality element considered to have 'minor' or 'serious' limitations was rated down by 1 or 2 points respectively. A quality assessment of 'Unclear' was added to the list of possible GRADE-CERQual levels. Together with the committee, it was decided that in qualitative reviews 1 'Unclear' rating did not mean an automatic downgrade of the evidence for this theme. However, 2 'Unclear' ratings were downgraded by 1. Footnotes were not used for the CERQual tables (see Table 11 in the full version of the guideline).

The details of the criteria used for each of the main quality elements are discussed further in sections 4.3.5.2.1 to 4.3.5.3.4 in the full version of the guideline.

Evidence Statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome or theme and encompass the following key features of the evidence:

The quality of the evidence (GRADE rating)
The number of studies and the number of participants for a particular outcome
A brief description of the participants
The clinical significance of the effect and an indication of its direction (for example, if a treatment is clinically significant [beneficial or harmful] compared with another, or whether there is no clinically significant difference between the tested treatments).

Evidence of Cost-effectiveness

The aims of the health economic input to the guideline were to inform the guideline committee of potential economic issues related to the diagnosis and management of cystic fibrosis to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on healthcare benefits (ideally in terms of quality-adjusted life-years (QALYs) with the costs of different care options. In addition, the health economic input aimed to identify areas of high resource impact; recommendations which – while nevertheless cost-effect – might have a large impact on CCG or Trust finances and so need special attention.

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature, as described above, new economic analysis was undertaken by the Health Economist in selected areas. The following priority areas for de novo economic analysis were agreed by the committee after formation of the review questions and consideration of the available health economic evidence:

Immunomodulatory agents in the management of lung disease,
Antimicrobial regimens in suppressing chronic pulmonary disease,
Configuration of services to minimise the risk of cross-infection.

A costing tool was also developed for the review question relating to models of care, where little clinical

evidence was uncovered. It was thought that the committee may wish to make recommendations that would lead to a high resource impact, although current practice was recommended.

The methods and results of de novo economic analyses are reported in Appendix K. When new economic analysis was not prioritised, the committee made a qualitative judgement regarding cost effectiveness by considering expected differences in resource and cost use between options, alongside clinical effectiveness evidence identified from the clinical evidence review. Cost descriptions used to aid considerations of cost effectiveness are also reported in Appendix K.

Cost-effectiveness Criteria

NICE's report Social value judgements: principles for the development of NICE guidance sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or;
- The intervention cost less than £20,000 per QALY gained compared with the next best strategy, or;
- The intervention provided clinically significant benefits at an acceptable additional cost when compared with the next best strategy.

The committee's considerations of cost-effectiveness are discussed explicitly in the 'Consideration of economic benefits and harms' section of the relevant sections.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC) and the National Institute for Health and Care Excellence (NICE): This guideline was developed by the National Institute for Health and Care Excellence (NICE) for the Department of Health. See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Who Developed This Guideline?

A multidisciplinary guideline committee comprising healthcare professionals and researchers as well as lay members developed this guideline (see the list of group members and acknowledgements).

The guideline committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Martin Walshaw in accordance with guidance from NICE. The group met every 4 to 6 weeks during the development of the guideline.

Staff from the NGA provided methodological support and guidance for the development process. The team working on the guideline included a guideline lead, a project manager, systematic reviewers, health economists, a statistician and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the group.

Developing Recommendations

Guideline Recommendations

Over the course of the guideline development process, the committee were presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature: all evidence tables are in Appendix H and economic evidence tables are in Appendix L
- Summary of clinical and economic evidence and quality assessment (as presented in Chapters 5 to 11)
- Forest plots (Appendix I)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix K).

Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally, in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes, although most of the reviews in the guideline were outcome driven. When this was done informally, the group took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the group's values and preferences) and the confidence the group had in the evidence (evidence quality). Secondly, the group assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The group also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The wording of recommendations was agreed by the group and focused on the following factors:

- The actions healthcare professionals need to take,
- The information readers of the guideline need to know,
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations),
- The involvement of patients (and their carers if needed) in decisions about treatment and care,
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective intervention.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others, depending on the quality of the underpinning evidence. The Committee makes a recommendation based on the trade-off between the benefits and harms of a system, process or an intervention, taking into account the quality of the underpinning evidence. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The Committee usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the Committee uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The Committee uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of people, a system, process or an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the Committee is confident that an intervention will not be of benefit for most people.

Interventions That Could Be Used

The Committee uses 'consider' when confident that a system, process or an intervention will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Cost Analysis

Refer to the "Economic evidence" and "Consideration of economic benefits and harms" sections in the full version of the guideline. Also see Appendices K to M for the health economic evidence, evidence tables, and quality assessment.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) Web site at publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The type of evidence supporting each review area is detailed in the full version of the guideline (see the "Availability of Companion Documents" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- By making robust recommendations based on the available evidence and best practice in cystic fibrosis care, this guideline will help improve care for this highly complex condition.
- Healthcare professionals working with people with cystic fibrosis suggested that monitoring the

transition process can help improve the experience of transition to adult services.
- Early recognition and management of upper airways disease can improve quality of life significantly.
- In addition to the benefits found by the general population, exercise participation is advised in cystic fibrosis to help maintain and slow the decline in respiratory function, facilitate airway clearance techniques, help improve bone mineral density and to increase and maintain muscle strength, flexibility and posture.
- Early detection of liver disease may prevent further damage and, in some case, may be reversible. Ultrasound can detect evidence of liver disease, for example changes in liver echogenicity as well as advanced changes suggestive of portal hypertension. It can also detect the presence of gallstones which sometimes occur in cystic fibrosis.
- People with cystic fibrosis would benefit in having a routine screen which would indicate those who require further psychological intervention. This would allow early intervention by a team psychologist to enable maintenance of good quality of life, prevention of the development of mental health disorders and improvement in health outcomes as a result of improved wellbeing.

Refer to the "Consideration of clinical benefits and harms" sections of the full version of the guideline (see the "Availability of Companion Documents" field) for details about benefits of specific interventions.

Potential Harms

- The committee stated that it was crucial the adverse effects of treatment were taken into consideration when making their recommendations as they may outweigh the benefits related to lung function and exacerbations the agents can provide.
- With increasing longevity come unexpected complications due to the side-effects of treatment regimens, as well as those associated with older age.

Refer to the "Consideration of clinical benefits and harms" sections of the full version of the guideline (see the "Availability of Companion Documents" field) for details about potential harms of specific interventions.

Qualifying Statements

Qualifying Statements

- The recommendations in this guideline represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The application of the recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.
- Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Implementation of the Guideline

Description of Implementation Strategy

Putting This Guideline into Practice

The National Institute for Health and Care Excellence (NICE) has produced tools and resources to help put this guideline into practice (see also the "Availability of Companion Documents" field).

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

- Raise awareness through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations.
- Identify things staff can include in their own practice straight away.
- Identify a lead with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.
- Carry out a baseline assessment against the recommendations to find out whether there are gaps in current service provision.
- Think about what data you need to measure improvement and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.
- Develop an action plan, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.
- For very big changes include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.
- Implement the action plan with oversight from the lead and the project group. Big projects may also need project management support.
- Review and monitor how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See the into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience

from NICE. Chichester: Wiley.

Implementation Tools

Clinical Algorithm

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Guideline Alliance. Cystic fibrosis: diagnosis and management. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct 25. 42 p. (NICE guideline; no. 78).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Oct 25

Guideline Developer(s)

National Guideline Alliance - National Government Agency [Non-U.S.]

Source(s) of Funding

The National Guideline Alliance (NGA) was commissioned by the National Institute for Health and Care Excellence (NICE) to undertake the work on this guideline.

Guideline Committee

Guideline Committee

Composition of Group That Authored the Guideline

Guideline Committee Members: Mandy Bryon, Senior Consultant Clinical Psychologist, Head of Psychological Services, Great Ormond Street Hospital for Children NHS Trust; Janis Bloomer, Paediatric Nurse Specialist (Children and young people) Cystic Fibrosis, Great North Children's Hospital Royal Victoria Infirmary; Sarah Collins, Cystic Fibrosis Specialist Dietitian, Nutrition & Dietetic Department, Royal Brompton Hospital; Alexander Darlington, Lay Member; Iolo Doull, Consultant Respiratory Paediatrician, Children's Hospital for Wales, Cardiff; Elaine Edwards, Advanced Physiotherapist, Sheffield Children's NHS Foundation Trust; Zoe Elliott, Lay Member; Andrew Jones, Consultant and Honorary Reader in Respiratory Medicine and Cystic Fibrosis, North West Lung Centre, University Hospitals South Manchester NHS Foundation Trust; David Lacy, General Paediatrician, Wirral University Teaching Hospital NHS Foundation Trust; Nichola MacDuff, Adult Specialist Nurse, Advanced Clinical Nurse Specialist & Lead Nurse, Black Country Adult CF Centre, Royal Wolverhampton NHS Trust; Helen McCabe, Principal Paediatric Dietitian - Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust; Helen Parrott, Physiotherapist, Clinical Specialty Lead, Adult CF Therapies Royal Brompton Hospital; Sarah Popple, Senior Pharmacist Paediatrics and Cystic Fibrosis University Hospitals of Leicester; Keith Thompson, Senior Respiratory Pharmacist, Royal Brompton and Harefield NHS Foundation Trust; Martin Walshaw (*Chair*), Consultant Physician in General and Chest Medicine at Royal Liverpool and Broadgreen University Hospitals NHS Trust, and The Liverpool Heart and Chest Hospital NHS Foundation Trust, Honorary Professor of Medicine at the University of Liverpool

Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all group members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent group meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest necessitated it appropriate to do so. The details of declared interests and the actions taken are shown in Appendix C (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

Cystic fibrosis: diagnosis and management. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct. 769 p. (NICE guideline; no. 78). Available from the National Institute for Health and Care Excellence (NICE) Web site .

Cystic fibrosis: diagnosis and management. Appendices. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct. (NICE guideline; no. 78). Available from the NICE Web site .

Cystic fibrosis: diagnosis and management. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct. (NICE guideline; no. 78). Available from the NICE Web site .

Cystic fibrosis: diagnosis and management. Resource impact statement. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct. (NICE guideline; no. 78). Available from the NICE Web site .

Developing NICE guidelines: the manual. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Oct. Available from the NICE Web site .

Patient Resources

The following is available:

Cystic fibrosis: diagnosis and management. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2017 Oct. (NICE guideline; no. 78). Available from the National Institute for Health and Care Excellence (NICE) Web site .

NGC Status

This NGC summary was completed by ECRI Institute on December 13, 2017. The guideline developer agreed to not review the content.

This NEATS assessment was completed by ECRI Institute on December 6, 2017. The guideline developer did not acknowledge or provide confirmation for this NEATS assessment.

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